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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,405	10/28/2003	Johanna Bentz	3139-6328.1US (ARC 3277 U	7380

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EXAMINER	
BARNHART, LORA ELIZABETH	

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
09/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/696,405	BENTZ ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14-17 and 19-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14-17 and 19-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 7/6/07 to claims 1, 15-17, and 30 have been entered. Claims 13 and 18 have been cancelled in this reply. No claims have been added. Claims 1-12, 14-17, and 19-35 remain pending in the current application, all of which are being considered on their merits. Prior art references not included with this Office action can be found in a prior action.

Election/Restrictions

Applicant's election without traverse of various species, including "pituitary adenylate cyclase polypeptide (PACAP)" as the polypeptide and "amino acid buffers" as the buffers in the reply filed on 10/30/06 is still in effect over the claims.

Claim Rejections - 35 USC § 102

The rejections of record under 35 U.S.C. § 102 are withdrawn in light of the amendments to the claims and applicant's comments.

Claim Rejections - 35 USC § 103

Any rejections of record under 35 U.S.C. § 103 not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments. The claim amendments necessitate the following new ground of rejection.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12, 14-17, and 19-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carpenter et al. (1989, U.S. Patent 4,806,343), Andya et al. (2001, U.S. Patent 6,267,958), Thomson (1989, U.S. Patent 4,816,440), Nishimura et al. (1999, U.S. Patent 5,861,284) and Arimura et al. (1992, U.S. Patent 5,128,242).

Carpenter et al. teach a composition comprising phosphofructokinase (PFK), a polypeptide; trehalose; and zinc ions, said composition being lyophilized to form a powder that stabilizes the activity of PFK (Example VII; column 6, lines 30-47). Specifically, the composition of Carpenter et al. comprises an aqueous solution of 0.025mg/mL PFK, 0.32mM $ZnSO_4$ (0.051mg/mL), and 60mM trehalose (20.5mg/mL). Therefore, the weight ratio of metal ion to polypeptide is 2.04:1, which is "about" 1:1, "about" 2:1, and "about" 4:1. The zinc ion in the composition of Carpenter et al. is "derived" from $ZnCl_2$ (as in claim 9) in that zinc chloride ionizes in water to yield zinc ion; the claim does not require that the recited divalent salts *per se* be present in the composition.

Carpenter et al. do not exemplify the ratios of trehalose to PFK recited in claims 5-7. Carpenter et al. do not exemplify a lyophilized composition comprising each and every metal ion recited in claim 9. Carpenter et al. do not teach a composition in which the surfactant is SDS. Carpenter et al. do not teach a composition in which the polypeptide is PACAP or any other polypeptide selected from the pituitary adenylate cyclase polypeptide/glucagon superfamily.

Andya et al. teach compositions comprising HER2 antibody, a polypeptide; trehalose, a sugar; TWEEN 20, a surfactant; and in some cases, histidine, an amino acid buffer, said composition being lyophilized to form a powder that stabilizes the activity of HER2 antibody (column 2, lines 4-41; Table 2, lines 7-14). Specifically, the compositions of Andya et al. comprise 21mg/mL HER2 antibody, 250mM trehalose (86mg/mL), 0.01% or 0.2% TWEEN 20 (10 or 200mg/mL), and 10mM histidine (1.55mg/mL).

Thomson teaches a composition comprising lyophilized interleukin-2, which is stable (column 9, lines 37-45). Thomson also teaches a lyophilized composition comprising interleukin-2 or interferon-beta and SDS (column 3, lines 30-39).

Nishimura et al. teach a composition for stabilizing polypeptides with an amide at their C-terminal or a disulfide linkage in the molecule, one of which is PACAP (column 4, lines 39-56, particularly lines 51-52). The composition of Nishimura et al. is lyophilized, *i.e.* it is a powder comprising particles (column 12, lines 53-63) and may further comprise trehalose (column 12, lines 23-26) as well as buffers, salts, and/or surfactants (column 12, lines 49-53).

Arimura et al. teach that PACAP and fragments thereof have therapeutic activity, for example in stimulating the pituitary (column 6, section 5.3 starting at line 45). A person of ordinary skill in the art would have had a reasonable expectation of success in including an amino acid buffer and/or a surfactant in the composition of Carpenter et al. because Andya et al. teach that amino acid buffers and surfactants may be included in lyophilized compositions comprising any of numerous diverse proteins. The skilled artisan would have been motivated to include amino acid buffers and/or surfactants because Andya et al. teach that these molecules protect the protein during the lyophilization and storage processes.

The selection of the amount of trehalose, metal ion, amino acid buffer, and/or surfactant to add to the composition of Carpenter et al. would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Carpenter et al. teach that the amount may be modified as necessary (column 3, lines 19-35). Furthermore, Andya et al. broadly teaches that proteins may be lyophilized with varying amounts of trehalose as necessary. A holding of obviousness over the cited claims is therefore clearly required.

The selection of the metal ion to include the composition of Carpenter et al. would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Carpenter et al. teach that the addition of calcium, magnesium, or zinc increases the activity of PFK in the composition compared to compositions lacking such metal ions (Example III; Table I; column 5, lines 5-31). A holding of obviousness over the cited claims is therefore clearly required.

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the SDS of Thomson for the surfactants of Andya et al. because Thomson teaches that SDS, like the surfactants of Andya et al., protect proteins from lyophilization. The skilled artisan would have been motivated to make this modification because Thomson teaches that SDS maintains the stability of lyophilized proteins.

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the PACAP of Nishimura et al. for the PFK of Carpenter et al. because Nishimura et al. teach that PACAP, like PFK, can be stably stored by lyophilizing a solution of the protein, trehalose, and salts; furthermore, Andya et al. teach that a diverse group of proteins can be preserved in such a compostion. The skilled artisan would have been motivated to make this substitution in order to preserve active PACAP, which Arimura et al. teach is a therapeutic protein for pituitary disorders, until it is needed to treat a patient.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to include amino acid buffers and/or surfactants in the composition of Carpenter et al. because Andya et al. teach that, like trehalose and metal ions, amino acid buffers and surfactants are lyoprotectants. It is well established that duplicating components with similar functions within a composition is obvious; see *In re Harza*, 274 F.2d 669, 124 USPQ 378 (CCPA 1960) and M.P.E.P. § 2144.04. It would have been further obvious to modify the amount of trehalose, metal ion, amino acid buffer, and/or surfactant and the character of the metal ion included in the

composition of Carpenter et al. because Carpenter et al. and Andya et al. suggest such optimization.

It would have been further obvious to a person of ordinary skill in the art at the time the invention was made to substitute the SDS of Thomson for the surfactants of Andya et al. because the two are functional equivalents, *i.e.* they protect proteins in lyophilized compositions. Therefore, these may be considered to be art-accepted equivalents.

It would have been further obvious to a person of ordinary skill in the art at the time the invention was made to substitute the PACAP of Nishimura et al. for the PFK in the composition of Carpenter et al. because Arimura et al. teach that PACAP is a valuable therapeutic biomolecule, and because Nishimura et al. teach that PACAP can be preserved in a composition similar to that of Carpenter et al.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant alleges that the cited art does not suggest that the compositions would be stable at temperatures up to or exceeding physiological conditions, as required by the claims (Reply, page 10, last paragraph). Applicant alleges that the cited prior art does not teach or suggest all of the limitations (Reply, page 11, paragraph 2). These arguments have been fully considered, but they are not persuasive.

First, the claimed composition is not required to be under any particular conditions. All that is required is that the composition comprise a polypeptide that is a member of the pituitary adenylate cyclase polypeptide/glucagon superfamily and a

stabilizing agent that is stable "under acidic conditions up to or exceeding physiological conditions." The claim does not require that the composition be at physiological conditions, as applicant seems to imply. The composition is necessarily characterized only by its pH, which, as the examiner reasons above, is optimizable.

Furthermore, applicant's comments about freeze-drying conditions are not persuasive because the claim requires that the composition be stable "up to or exceeding" physiological conditions, *i.e.*, at any temperature and under any conditions. In other words, if "physiological conditions" is interpreted as being "37°C," the claim requires that the protein be stable at "up to or exceeding 37°C," a limitation that includes freezing temperatures. The same argument applies to the degree of moisture in the composition; "up to a physiological level of moisture" encompasses "dry." Therefore, the claims are sufficiently broad as to encompass all compositions that comprise pituitary adenylate cyclase polypeptide/glucagon superfamily polypeptides; that further comprise some stabilizer; and that are stable under any conditions and that are acidic, regardless of temperature and moisture content as well as any other physiological parameters. None of the dependent claims particularly limits the conditions under which the composition is stable.

In response to applicant's arguments against the Nishimura and Arimura references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The Nishimura and Arimura references were relied

upon for their teachings of stabilized PACAP compositions and the activity of PACAP, respectively. The claimed invention becomes obvious when all of the cited references are considered together, as set forth above by the examiner.

No claims are allowed. No claims are free of the art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lora E Barnhart